PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 9/70

A1

(11) International Publication Number: WO 89/10740

(43) International Publication Date: 16 November 1989 (16.11.89)

(21) International Application Number: PCT/GB89/00491

(22) International Filing Date: 9 May 1989 (09.05.89)

(30) Priority data:
8810951.7 9 May 1988 (09.05.88) GB

(71) Applicant *(for all designated States except US)*: INNOVATA BIOMED LIMITED [GB/GB]; 18 Dublin Street, Edinburgh EH1 3PT (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : BOYES, Robert, Nichol [CA/GB]; 6 Lancaster Road, St Albans, Herts AL1 4ET (GB). PERKINS, Brenda [US/US]; 512 Avenue V, Birmingham, AL 35214 (US). STROBEL, Janna, N. [US/US]; 217 Honeybee Circle, Trussville, AL 35173 (US). DUNN, Richard, L. [US/US]; 1625 Sharp Point Drive, P.O. Box 460, Fort Collins, CO 80522 (US).

(74) Agents: WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU (GB).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB, GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: BUCCAL LOCAL ANAESTHETIC

(57) Abstract

An anaesthetic patch suitable for use in the mouth is disclosed, which comprises a biocompatible hydrophilic polymer matrix loaded with an anaesthetic, which matrix is capable of adhering directly to the oral mucosa without an adhesive, and an impermeable inert support membrane.

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BUCCAL LOCAL ANAESTHETIC

This invention relates to an anaesthetic patch for use in the mouth.

Local anaesthesia for dental procedures is usually provided by parenteral injection of a suitable local anaesthetic product such as lignocaine or prilocaine. In some cases, these drugs are formulated in ointments, creams, gels or aerosol sprays to be applied to the gums to provide local pain relief. All of these anaesthetic procedures have significant disadvantages from both a medical and a patient acceptance point of view. Parenteral injections are difficult to administer, are extremely uncomfortable for the patient, are occasionally associated with serious adverse reactions and, in general, the anaesthesia lasts for a prolonged period after the dental procedure, causing unpleasant numbness in the lips and tongue of the patient. The various topical products are rapidly removed from their site of application in the mouth by the saliva and, as a result, the duration of their effect is very short. Furthermore, the anaesthetic is free to diffuse throughout the mouth and, thereby, causes an unpleasant taste as well as discomforting numbness in the tongue.

According to the present invention there is provided an anaesthetic patch for use in the mouth, which patch comprises a film comprising a biocompatible, hydrophilic polymer matrix loaded with an anaesthetic, which matrix is capable of adhering directly to the oral mucosa without an adhesive and an impermeable inert support membrane.

Optionally the anaesthetic patch includes a third component in the form of a release liner, which is positioned over the loaded matrix to keep the matrix clean prior to use of the patch. This liner is removed immediately before application of the patch to the oral mucosa.

Typically the release liner comprises silicone-

treated paper.

It is therefore possible in accordance with the invention to provide a device which concentrates the local anaesthetic to a specific site on the gums and which does not allow drug to diffuse into the mouth in general. The patch may not only provide concentrated anaesthetic effect to the site of application but that effect can also continue until the device is removed. The patch may allow anaesthetic agent to penetrate the gingival mucosa and reach the nerves which transmit painful stimuli from the tooth. The patch can therefore be employed to provide anaesthesia for operative procedures of the gums as well as for restorative procedures of the teeth themselves.

The patch incorporates a film comprising a biocompatible, hydrophilic polymer matrix loaded with anaesthetic. The film should have good adhesive properties, i.e. good wet tack, as the patch must adhere directly to the oral mucosa through the surface of the film not provided with a backing material. Wet tack may be determined by pressing a moist finger onto the surface of the film and then observing the adhesion of the film to the finger.

Suitable polymers for the matrix include sodium carboxymethyl cellulose (CMC), poly(vinyl pyrrolidone) (PVP), copolymers of methyl vinyl ether and maleic anhydride such as Gantrez (trade mark) ES-225 and an acrylic latex such as Rhoplex (trade mark) NB-560. Preferred polymers are polymers from which soft and flexible films may be formed. Such films are most practical for use in the mouth. Preferred polymers are therefore PVP and copolymers of methyl vinyl ether and maleic anhydride. PVP's are generally used having molecular weights from 20000 to 700000, typically from 40000 to 360000, for example PVP-40, PVP K-60 and PVP K-90 having molecular weights of 40000, 160000 and 360000 respectively. The low molecular weight PVP K-29/32 (having a molecular weight of in the region of 30000) may also be used. Although polymers of lower

molecular weight have the potential to impart greater flexibility to the patch than those of higher molecular weight, PVP K-90 combines a satisfactory degree of flexibility with strength and is therefore particularly suitable.

A non-toxic plasticiser may be incorporated into the polymer matrix to improve the softness and flexibility of the final patch. Suitable plasticisers include sorbitol and glycerol. Glycerol is generally preferred since it has a higher solubility in the solvents used in the preparation of the anaesthetic-loaded patch. The plasticiser may be incorporated in any amount, within the limits of its solubility, and is typically used in an amount of from 0.01 to 15% of the total weight of the anaesthetic-loaded matrix. For example, sorbitol is suitably used in an amount of 0.5% by weight and glycerol is suitably used in an amount of 5% by weight.

When the polymer matrix of the patch comprises more than one polymer, for example two, it is possible for the second polymer to act as a plasticiser within the composition. One example of a patch within the invention comprises a polymer matrix consisting of the anaesthetic lidocaine, two PVP's (PVP K-90 and PVP K-29/32) and glycerol in a weight ratio of 25:45:25:5. The PVP K-29/32, having a lower molecular weight than the PVP K-90, acts as a plasticiser in addition to the glycerol.

The anaesthetic provided in the patch may be a local anaesthetic, although the patches can be employed to deliver systemic anaesthetics too. An amide anaesthetic may be employed such as lignocaine (lidocaine), prilocaine, carbocaine, bupivacaine or etidocaine. The anaesthetic may be employed in free form or in the form of an acid addition salt, typically the hydrochloride. In particular, lignocaine or lignocaine hydrochloride is used.

The support membrane of the patch is inert and impermeable. The membrane generally comprises polyurethane,

for example it is a polyester/polyurethane film or foam, and is typically coated with an acrylic adhesive. The anaesthetic-loaded polymer matrix adheres in this case to the acrylic adhesive coating which, in turn, is relatively impermeable to the anaesthetic. The side of the membrane opposite to that coated with adhesive presents a smooth, non-sticky surface to the oral cavity, protecting and supporting the patch as a whole. The support membrane may be formed by laminating an acrylic adhesive, such as TT5022-00 available from Semex Medical, Frazer PA, US to a polyurethane which is in the form either of a thin film or a slightly thicker foam. A maximum thickness for the polyurethane film is generally about 63.6 μm (2.5 mil) whereas for the foam the maximum thickness is generally 762μm (30 mil).

Alternatively a commercially available support membrane may be used. Particularly suitable is KM1354-00, from Semex Medical, a polyester/polyurethane film coated with an acrylic adhesive. This typically comes provided with a silicone-treated release liner which protects the adhesive side of the membrane. A further example of a suitable membrane is KM-1952, an acrylic adhesive/polyurethane foam also from Semex Medical.

The support membrane is impermeable so that water and saliva can not penetrate into the patch and thereby allow anaesthetic to leach out through the surface which does not adhere to the oral mucosa. The support membrane is therefore typically coterminous in area with the polymer matrix film loaded with anaesthetic. This has the additional effect of ensuring a unidirectional flow of anaesthetic into the tissue of the mouth to be anaesthetised.

The third, and optional, component in the patch of the present invention is a release liner which is placed over the anaesthetic-loaded matrix. The liner serves both to keep the matrix clean and to prevent individual patches

from adhering to each other when packaged. The liner is typically a silicone-treated paper and a suitable example is 3402 available from Semex Medical, Frazer, PA. This particular product comes provided with a support membrane, although it is not essential to the invention that the release liner be supplied together with a support membrane.

The anaesthetic is suitably incorporated in the polymer matrix in an amount of from 1 to 30% by weight. The proportions may vary in this range depending upon the type of anaesthesia it is desired to induce. For anaesthesia of soft tissue, therefore, the film typically incorporates from 2 to 15% by weight of anaesthetic. For anaesthesia of deep tissue, the film typically comprises from 15 to 25% by weight of anaesthetic. The amount of anaesthetic will also depend upon the potency of the anaesthetic, however. For lignocaine either as the free base or as the hydrochloride, for example, from 5 to 30 mg of anaesthetic may be incorporated per cm^2 of the surface area of a patch.

The patches of the invention are suitably prepared by casting. In a preferred method, which is both economical and continuous, a doctor blade is used. This method comprises dissolving the anaesthetic and the matrix polymer in an appropriate inert solvent such as water, ethanol or acetic acid. Ethanol is particularly suitable. The resulting solution is then placed at one end of a casting substrate and a doctor blade is moved across the solution for the length of the casting substrate to spread the solvent blend evenly over the casting substrate. The solvent then evaporates off.

The casting substrate may be either the support membrane itself or, alternatively, the release liner. It is particularly convenient to use the release liner as casting substrate and to attach the support membrane to the polymer matrix charged with anaesthetic in a subsequent step to form a complete patch.

The doctor blade used in this casting method may be

any length, for example about 20 cm (or approx 8 in). The height of the blade is generally adjustable. Altering the weight has the effect of varying the thickness of the film formed on the casting substrate. The thickness of the film contributes to determining the content of anaesthetic in the final patch.

Besides adjusting the height of the doctor blade, an alternative means of controlling the thickness of the film on the casting substrate is by adjusting the viscosity of the casting solution. This may be done, for example by varying the content of ethanol in the solution.

The softness and flexibility of the final patch is increased by incorporating one or more plasticisers into the casting solution. Examples of suitable plasticisers include glycerol, sorbitol and fructose. Glycerol is particularly suitable, and is typically used at a concentration of 5wt%.

As an alternative to the doctor blade method of casting, the solution comprising the matrix polymer and the anaesthetic dissolved in a suitable solvent is simply poured into an open container, whereupon the solvent evaporates off. The resulting film is then provided with a support membrane, typically by adhesion.

The patches may be of any appropriate size or shape. Typically they may range in size from 1 to 5 cm^2, preferably from 1 to 2 cm^2. They may be circular, oval, square or rectangular. The thickness of the patch excluding the release liner is generally from 0.1 mm to 0.5 mm, for example from 0.157 mm to 0.464 mm. Taking the release liner into account the overall thickness is typically from 0.2 mm to 0.7 mm, for example from 0.227 to 0.627.

In a first embodiment of the invention, the patch is about 1.3 x 2.5 cm in area and comprises, as support membrane, a polyurethane-containing film (such as KM 1354-00 from Semex Medical); an anaesthetic-releasing film comprising about 25 mg lidocaine, about 25 mg of a poly(vinyl-pyrrolidone) polymer (such as PVP K-90 from Semex

Medical) and about 25 mg of glycerol; and, as release liner, a silicone-treated paper of which a suitable example is 3402 from Semex Medical.

In a second embodiment, the patch differs from that of the first embodiment in that the anaesthetic releasing film comprises about 25 mg of lidocaine, about 32 mg of a PVP and about 14 mg of glycerol. This patch has less dry tack than the first.

In use, the patch is applied to the buccal mucosal or gingival region in need of anaesthetising. The patch adheres via the exposed surface of the polymer matrix film loaded with anaesthetic. Typically, the patch is positioned to cover the cervical margin of the tooth and its attached mucosa. It is therefore usually located away from the gingival margins.

The following Examples illustrate the invention. In the accompanying drawings:

Figure 1 shows the average cumulative fraction of lidocaine. HCl released from various films in the in vitro evaluation in Example 1;

Figure 2 shows the average cumulative fraction of lidocaine from various films in the in vitro evaluation in Example 2;

Figure 3 shows the average cumulative fraction of lidocaine released from PVP K-60 film in Example 2 which was sealed in polyurethane film or not;

Figure 4 shows the effect of a lidocaine.HCL-containing film on the electrical stimulation threshold of teeth in Example 3;

Figure 5 shows the in vitro release characteristics of lidocaine patches tested in Example 5, wherein the line marked ■ denotes the use of a buffer at pH 7.3 as receiving fluid and the line marked ▲ denotes pure water as the receiving fluid;

Figure 6 shows the in vitro release characteristics of lidocaine patches tested in Example 6, and neat lidocaine tested in the Comparative Example, wherein the line marked ● denotes neat lidocaine, the line marked ■ denotes a patch containing 5.5 mg lidocaine and ▲ denotes a patch containing 12.6 mg lidocaine;

Figure 7 shows the in vitro release characteristics of lidocaine patches tested in Example 7, wherein the line marked ● denotes a patch incorporating sorbitol as a plasticiser and ■ denotes a patch without plasticiser;

Figure 8 illustrates the in vitro release characteristics of patches wherein the lidocaine film has two different thicknesses: the line marked ● denotes a thickness of 0.030 cm and ■ denotes 0.044 cm; and

Figure 9 illustrates the in vitro release characteristics of patches of different surface area, wherein the line marked ● denotes a patch of 3.25 cm^2 and ■ denotes one of 1.00 cm^2.

Example 1: Preparation and in vitro evaluation of lidocaine.HCl-loaded films

Films containing lidocaine.HCl were prepared from sodium carboxymethyl cellulose (CMC), Gantrez ES-225, polycaprolactone (PCL), PVP-40 and PVP K-60 by solvent casting in an open container at 50°C or at room temperature. Film preparation consisted of dissolving 25% lidocaine.HCl and 75% of the polymeric excipient in either water, ethanol or acetic acid. The solution was poured into an open container that was lined with either Mylar (trade mark) or Teflon (trade mark). The solvent was evaporated at 50°C or at room temperature. Films prepared with PVP, PCL and Gantrez were soft and flexible, while those prepared from CMC were harder and more rigid. Dry or wet tack was determined by pressing either a dry or a moist finger onto the surface of the film and then observing the adhesion of the film to the finger. The results from the various films

are summarised in Table 1.

TABLE 1 : LIDOCAINE.HCL-LOADED[a] FILMS

Sample No. E088	Film-forming polymer	Film thickness,[b] mm	Dry tack	Wet tack
-37-1	Gantrez ES-225	0.781	No	Yes
-38-1	CMC	0.299	No	Yes
-39-1	PVP K-60	0.813	Yes	Yes
-40-1	PVP-40	ND[c]	No	Yes
-42-1	PCL	ND	No	No

[a] All films contained 25 wt% lidocaine.HCl.
[b] Film thickness was determined with a micrometer.
[c] ND = not determined.

In vitro release experiments were carried out in triplicate using 1 cm^2 samples of each film. Release from the films was allowed from only one surface by applying a poly(methyl methacrylate) (PMMA) backing to one side of the sample. The in vitro release of lidocaine.HCl was then determined by immersing the samples in separate containers of Sorensen's phosphate buffer. The sealed containers were incubated at 37°C and agitated at low speed in a shaker bath. Samples for analysis of lidocaine were removed at 5, 10, 20, 30 and 60 minutes. The quantity of lidocaine.HCl released was determined in these samples spectrophotometrically. Figure 1 shows the average cumulative fraction of lidocaine.HCl released from various films.

Example 2: Preparation and in vitro evaluation of lidocaine-loaded films

Films containing lidocaine were prepared from PCL, PVP-40, PVP K-60, PVP K-90, Gantrez ES-225 and Rhoplex N-560 by solvent casting with a high-speed centrifugal spin caster. The preparation of blends for film formation was the same as that described for lidocaine.HCl. The lidocaine/polymer solution was injected with syringe into a spin-casting cup that was 8.9 cm (3.5 in.) in diameter, 7.6 cm (3.0 in.) deep and Mylar- or Teflon-lined. The cup was rotated at 3600 rpm until the solvent had evaporated. Then, the cylindrical film was removed from the cup and cut transversely to give a uniform, rectangular film. A film of CMC and 25% of lidocaine film was also prepared by dissolving the lidocaine and CMC in an ethanol/water mixture and solvent casting as described in Example 1. The results from the various films are summarised in Table 2.

TABLE 2 : LIDOCAINE-LOADED[a] FILMS

Sample No. E088	Film-forming polymer	Film thickness,[b] mm	Dry tack	Wet tack
-18-1	PCL	0.678	No	No
-19-1	PVP-40	0.518	No	Yes
-20-1	CMC	ND[c]	No	Yes
-48-1	PVP K-60	0.627	No	Yes
-52-1	PVP K-90	0.510	No	Yes
-76-1	Gantrez ES-225	0.497	No	Yes
-82-1	Rhoplex N-560	ND	Yes	No

[a] All films contained 25 wt % lidocaine.

[b] Film thickness was determined with a micrometer.

[c] ND = not determined.

In vitro release experiments were carried on 1 cm^2 samples of each film except CMC and Rhoplex N-560 in the same way as in Example 1. To limit the release of lidocaine to one surface of the sample, the sample was secured to a PMMA backing or to a polyurethane film via a medical grade adhesive. Figure 2 shows the average cumulative fraction of lidocaine released from the films.

In order to make a useful anaesthetic device, it was essential to have an impermeable backing material for the drug-loaded film. An experiment was carried out in which the PVP K-60 film containing lidocaine was completely sealed in polyurethane film. Unsealed and sealed material was then subjected to in vitro release studies as described previously. The results are presented in Figure 3. These show that only negligible amounts of lidocaine were able to penetrate the polyurethane film.

Example 3: In vivo evaluation of lidocaine.HCl-loaded PVP K-60 films

The clinical benefits of these films were evaluated in a study involving 9 human volunteers. In each subject a lidocaine-containing film and a placebo film were placed on contralateral sites on the gingiva. The films remained in place for 30 minutes. Anaesthesia of the mucosa was evaluated using a sharp probe. Conduction anaesthesia of the teeth was evaluated by measuring the electrical stimulation threshold of an appropriate tooth. Data describing the onset and duration of the soft tissue anaesthesia are presented in Table 3. The effect of the lidocaine-containing film on the electrical stimulation threshold of the teeth is presented in the accompanying Figure 4.

TABLE 3 : Changes in soft tissue sensation.

Sensory change	Time mins	S.D. mins
Mucosa analgesic	7.4	3.4
Onset of lip paraesthesia	11.0	3.7
Return of normal sensation after patch removed		
Mucosa	26.4	8.9
Lip	22.6	5.2

It is clear from these data that the lidocaine-containing films with a polyurethane backing produce anaesthesia of the mucosa which is of considerable depth and rapid onset. Furthermore, this anaesthesia remains localized to the area of application, and the strong unpleasant taste of the drug is not observed. The observed changes in conduction threshold indicate that application of lidocaine films designed in this manner can produce varying degrees of conduction anaesthesia of the teeth.

Example 4: Preparation of lidocaine loaded film by doctor blade method of casting

Films comprising lidocaine as the anaesthetic were prepared from PVP K-90 and a combination of PVP K-90 and PVP K-29/32. Ethanol was used as the casting solvent and the casting substrate was either the release liner, or a support membrane comprising one or two layers of KM 1345-00, an acrylic adhesive/polyester polyurethane from Semex Medical.

The film was cast using a doctor blade in a fabrication box approx 76 cm x 35.5 cm x 15 cm (30" x 14" x 6") having a built-in manifold of five individually adjustable values to enable the flow rate and dispersion of nitrogen to be regulated. The composition of the casting solutions and the process conditions used are shown in Table 4.

TABLE 4

PREPARATION OF LIDOCAINE LOADED FILM BY DOCTOR BLADE METHOD OF CASTING

Sample	Composition of casting solution[a] wt % lidocaine/PVP[b]/plasticizer[c]	Process conditions: Casting substrate	Process conditions: Blade ht, mil
E088-132-03	25/75/0	Support membrane (1)[g]	
E088-133-01	25/75/0	Support foam[h]	130
E088-133-02	25/75/0	Support foam	90
E088-139-01	25/75/0	Support membrane (1)	75/75[j]
E088-140-01	10/90/0	Support membrane (1)	75/75
E088-142-01	25/74.5/0.5[k]	Support membrane (1)	75
E088-142-02	25/74.5/0.5[k]	Support membrane (1)	75
F092-011-01	25/70/5	Support membrane (2)	75
F092-013-01	25/75/0	Support membrane (2)	75/100
F092-020-01	25/72/3	Support membrane (2)	50/100
F092-022-01	25/74/1[k]	Support membrane (2)	50/100
F092-024-01	25/75/0	Support membrane (2)	50/100
F092-025-01	25/75/0	Release liner	100
F092-027-01	25/72/3	Support membrane (1)	75
F092-029-01	25/70/5	Support membrane (2)	75
F092-030-01	25/74/1[k]	Support membrane (2)	75
F092-043-01	25/(50:25)/0	Release liner	100
F092-044-01	25/(45:25)/5	Release liner	100
F092-045-01	50/50/0	Release liner	100
F092-046-01	50/45/5	Release liner	100
F092-047-01	25/(50:25)/0	Release liner	100
F092-048-01	25/(45:25)/5	Release liner	100
F092-049-01	50/50/0	Release liner	100
F092-050-01	50/45/5	Release liner	100
F092-053-01	25/75/0	Release liner	84
F092-056-01	50/45/5	Release liner	51
F092-056-02	50/45/5	Release liner	51
F092-057-01	50/45/5	Release liner	51
F092-058-01	50/45/5	Release liner	51
F092-059-01	50/45/5	Release liner	51
F092-060-01	50/45/5	Release liner	84
F092-065-01	25/(45:25)/5[m]	Release liner	84

TABLE 4 (continued)

Sample	N_2 flow rate, SCFH [d]	Drying time, hr [e]	Lidocaine-releasing film thickness, mm	Patch loading,[f] mg of lidocaine
E088-132-03	20	2	0.30	29
E088-133-01	20	2	ND[i]	ND
E088-133-02	20	2	0.18	16
E088-139-01	20	3	0.44	41
E088-140-01	20	3	0.48	18
E088-142-01	20	2	0.28	23
E088-142-02	20	2	0.23	15
F092-011-01	20	2	ND	ND
F092-013-01	20	4	0.39	39
F092-020-01	20	4	0.40	34
F092-022-01	20	4	0.31	21
F092-024-01	20	4	0.51	55
F092-025-01	20	2	0.41	36
F092-027-01	20	1	0.45	42
F092-029-01	20	1	0.28	27
F092-030-01	20	1	0.37	41
F092-043-01	4/10	6	0.45	78
F092-044-01	4/10	6	0.39	27
F092-045-01	4/10	6	0.39	77
F092-046-01	4/10	6	0.33	52
F092-047-01	10	2	0.39	38
F092-048-01	10	2	0.47	37
F092-049-01	10	2	0.53	78
F092-050-01	10	2	0.52	80
F092-053-01	10	2	0.29	25
F092-056-01	10	1	0.12	20
F092-056-02	10	1	0.16	35
F092-057-01	10	1	0.13	26
F092-058-01	10	3	0.13	20
F092-059-01	10	3	0.14	20
F092-060-01	10	2	0.40	50
F092-065-01	10	2	0.44	ND

Footnotes to Table 4

a Casting solutions contained 30 wt % solids (lidocaine, PVP, plasticizer) and 70 wt % ethanol, unless otherwise noted.

b PVP = PVP K-90 or a blend of PVA K-90 and PVP K-29/32 (w/w).

c Plasticizer = Glycerol, unless otherwise noted.

d SCFH = Standard cubic feet per hour.

e Rounded off to nearest hour.

f Lidocaine loading in a 3.25 cm^2 patch (1.3 x 2.5 cm). The lidocaine loading was calculated using the weight of the patch and the initial lidocaine concentration in the casting solution. (It was assumed that the patch did not contain residual ethanol.)

g Trade Name = KM1352-00 (Semex Medical, Frazer, PA), a polyurethane film coated with an acrylic adhesive. Number in parenthesis indicates number of layers.

h Trade Name = KM1952-00 (Semex Medical, Frazer, PA), a polyurethane foam coated with an acrylic adhesive.

i ND = Not determined.

j --/-- indicates two film layers were cast. The first layer was allowed to dry (about 1/2 the drying time), and then the second layer was cast on top of the first.

k Plasticizer = sorbitol.

l Casting solution contained 40 wt % solids and 60 wt % ethanol.

m Casting solvent was water, solids/water, 30:70 (w/w).

Example 5 In vitro evaluation of lidocaine patches produced by doctor blade casting

Patches loaded with 8.9 mg of lidocaine were suspended in purified water, at 37°C under infinite sink conditions, in an individual wire mesh cage to ensure that the lidocaine-loaded film was exposed at all times to the receiving fluid. Each sample was placed in an Eberbach shaker bath (Eherbach Corp; Ann Arbor, MI) and agitated at 60 or 120 oscillations per minute (OPM). Periodically the caged patches were transferred to fresh water. Samples of the water exposed to the patches (the receiving fluid) were quantified for lidocaine by UV spectophotometry.

The above-described process was repeated using Sorensen's phosphate buffer (pH = 7.3) instead of water as the receiving fluid.

Figure 5 shows the release kinetics of the lidocaine patches tested as described above. They are seen to be very similar.

Example 6: Effect on in vitro release kinetics of the loading of the patch

Patches 1 cm^2 in area were prepared by the method of Example 4, and were loaded with 12.6 mg or 5.5 mg of lidocaine (corresponding, respectively, to 25 wt% and 10 wt% of lidocaine in the film). Their in vitro release characteristics were evalluated by the process of Example 5, using deionised water at 37°C as the receiving fluid and an Eberbach shaker bath agitated at 60 oscillations per minute.

Figure 6 shows the dissolution profiles obtained. A change in the lidocaine loading appears to have little effect on the amount of lidocaine released from the patch.

Comparative Example: Release characteristic of neat lidocaine

Three samples of neat lidocaine, weighing 9.5 mg, 9.0 mg and 5.3 mg respectively were evaluated in vitro and

dissolution profiles established. The results are shown in Figure 5, from which a comparison with the dissolution profiles obtained with two loaded patches indicates that the polymer matrix in the patches is exercising a control over lidocaine release.

Example 7: Effect on in vitro release characteristics of lidocaine from a patch of a plasticiser

To illustrate the effect of a plasticiser on lidocaine release from a patch, two patches were prepared by the method of Example 4, one including the plasticiser sorbitol in the polymer matrix:

Lidocaine per patch (mg)	Sorbitol (mg)	(wt%)
4.6	0.46	0.5
8.9	0.00	0.0

Figure 7 shows that sorbitol slightly increases lidocaine release. However, sorbitol is not ideal since its low solubility in the casting solution makes it impossible to incorporate more than 1% by weight in the patch. Glycerol has proved to be a preferably plasticiser since it may readily be incorporated in higher concentrations, typically 5% by weight.

Example 8: Effect of the lidocaine-releasing film thickness on in vitro release characteristics

Patches 1 cm^2 in area were prepared by the method of Example 4.

Patch	Lidocaine per patch (mg)	Film thickness (cm)
1	8.9	0.030
2	12.6	0.044

They were tested by the process of Example 5 using deionised water at 37°C as receiving fluid and a shaker bath agitated at 60 oscillations per minute.

Figure 8 shows the dissolution profiles obtained, which indicate that a decrease in film thickness leads to an increase in lidocaine release. The difference in this particular instance appears to be only slight, although overall the thickness of the lidocaine film is observed to be one of the most important parameters in determining the total dose of lidocaine from a patch.

Example 9: Effect of surface area on release characteristics

Two patches of different surface area were prepared by the method of Example 4, as follows:

Patch	Surface area (cm^2)	Lidocaine loading (mg)
1	3.25 (1.3x2.5cm)	41.0
2	1.00 (1.00x1.00cm)	12.6

Their in vitro release characteristics were determined by the process of Example 5, using deionised water at 37°C as the receiving fluid and a shaker bath agitated at 60 oscillations per minute.

The results are shown in Figure 9, from which it is seen that an increase in surface area leads, as might be expected, to an increase in lidocaine release.

CLAIMS

1. An anaesthetic patch suitable for use in the mouth, which comprises a biocompatible hydrophilic polymer matrix loaded with an anaesthetic, which matrix is capable of adhering directly to the oral mucosa without an adhesive, and an impermeable inert support membrane.

2. An anaesthetic patch according to claim 1 which includes a release liner positioned over the matrix loaded with anaesthetic.

3. An anaesthetic patch according to claim 1 wherein the impermeable inert support membrane is coterminous in area with the matrix loaded with anaesthetic.

4. An anaesthetic patch according to claim 1 wherein the polymer matrix includes one or more plasticisers.

5. An anaesthetic patch according to claim 4 wherein the polymer matrix includes glycerol or sorbitol.

6. An anaesthetic patch according to claim 1 wherein the polymer matrix comprises poly(vinylpyrrolidone) or a copolymer of methyl vinyl ether and maleic anhydride.

7. An anaesthetic patch according to claim 1 wherein the anaesthetic is lidocaine or lidocaine hydrochloride.

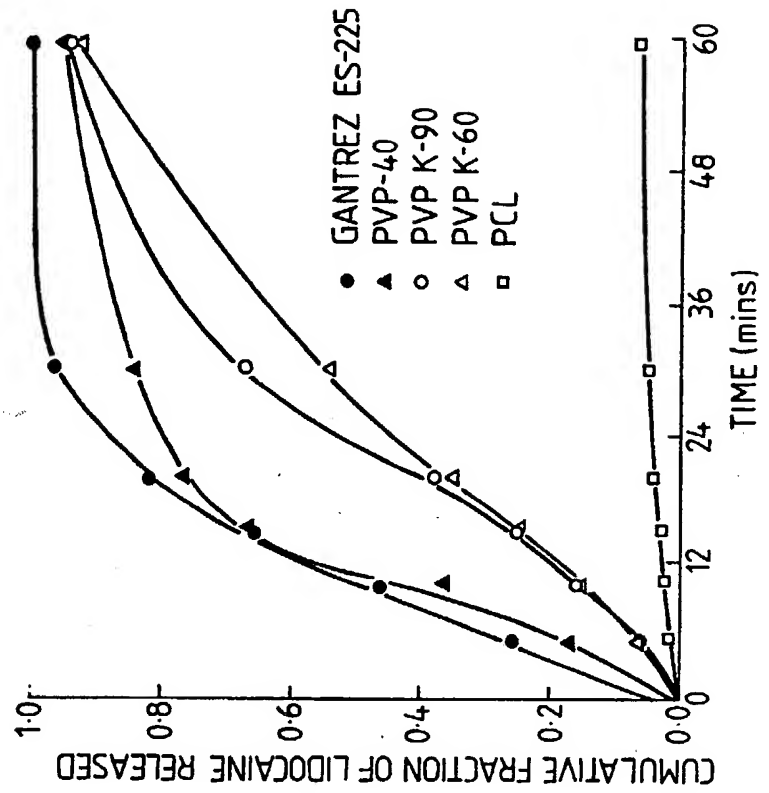
8. A method for producing an anaesthetic patch as claimed in claim 1 which comprises dissolving the anaesthetic and the hydrophilic polymer matrix in an inert solvent, spreading the resulting solution on a casting substrate by means of a blade and allowing the solvent to evaporate off.

9. A method according to claim 8 wherein the casting substrate is the release liner and wherein the support membrane is attached to the side of the loaded polymer matrix opposite to the release liner in a subsequent step.

10. A method of anaesthetising the buccal mucosa or the gingival region in a human or animal patient which

comprises applying to the mucosae or region in need of anaesthetising an anaesthetic patch as claimed in any one of claims 1 to 8, or a patch produced by the method as claimed in claim 9.

Fig. 2.


CUMULATIVE FRACTION OF LIDOCAINE RELEASED
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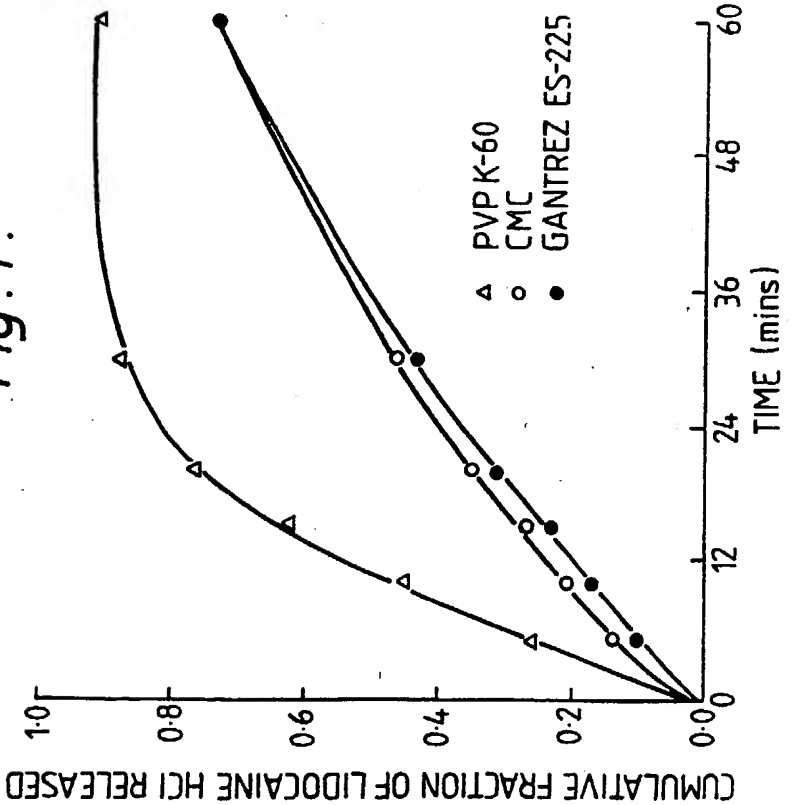
0·2
0·4
0·6
0·8
1·0
0
12
24
36
48
60
TIME (mins)
GANTREZ ES-225
PVP-40
PVP K-90
PVP K-60
PCL

Fig. 1.


CUMULATIVE FRACTION OF LIDOCAINE HCl RELEASED
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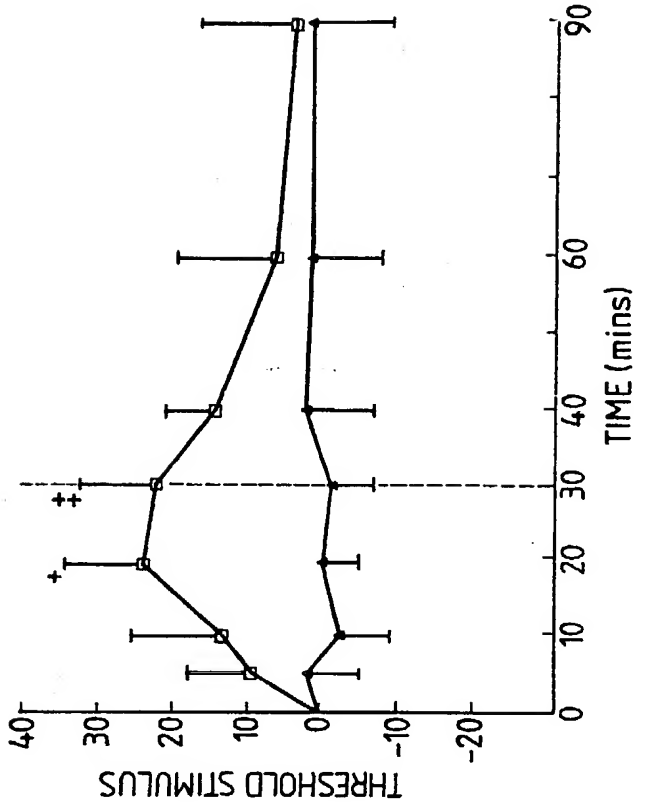
0·4
0·6
0·8
1·0
0
12
24
36
48
60
TIME (mins)
PVP K-60
CMC
GANTREZ ES-225

Fig. 4.


THRESHOLD STIMULUS
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30
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10
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-10
-20
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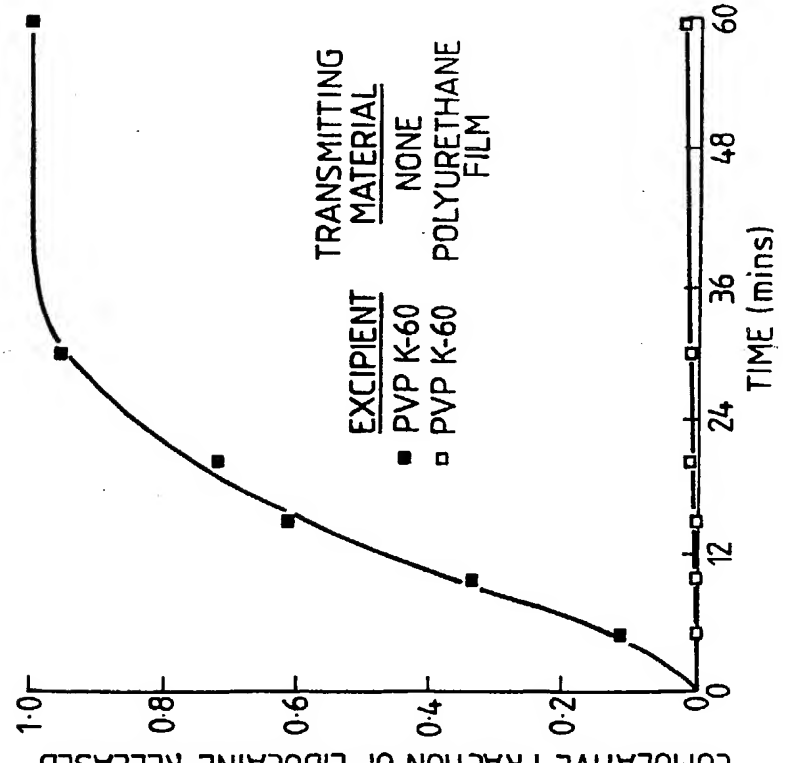
30
40
60
90
TIME (mins)
+
++

Fig. 3.


CUMULATIVE FRACTION OF LIDOCAINE RELEASED
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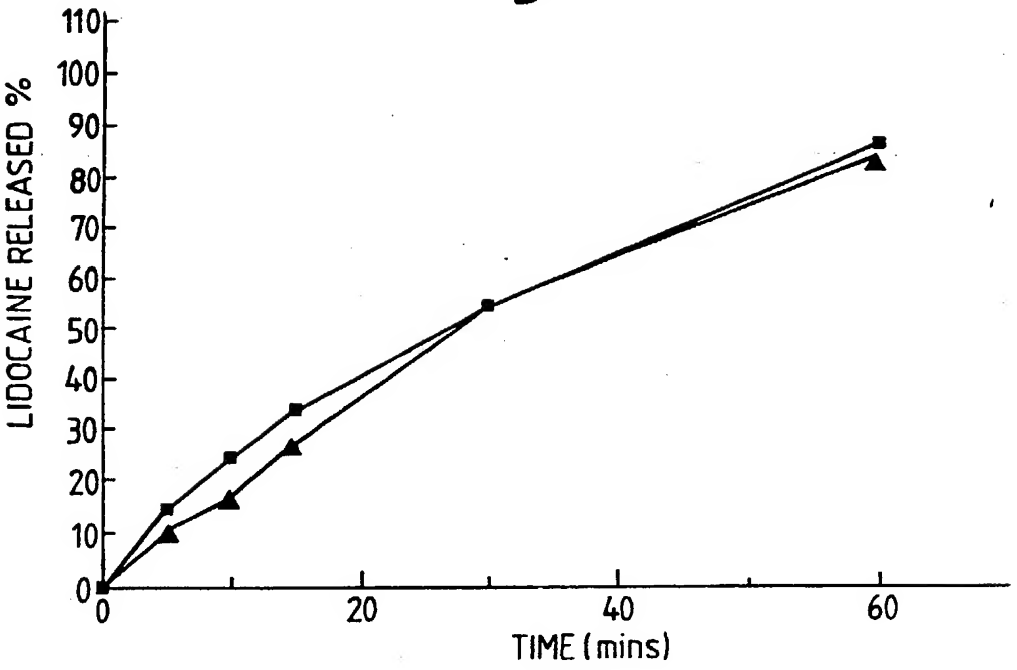
0·6
0·4
0·2
0
0
12
24
36
48
60
TIME (mins)
EXCIPIENT
PVP K-60
PVP K-60
TRANSMITTING MATERIAL
NONE
POLYURETHANE FILM

Fig. 5.


LIDOCAINE RELEASED %
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60
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40
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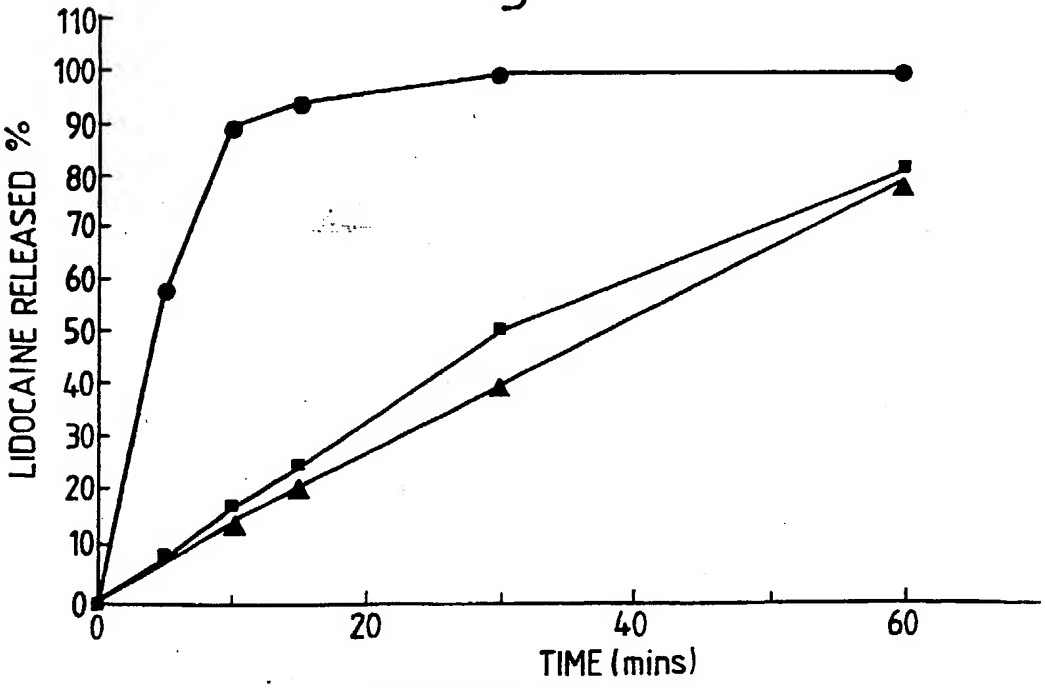
0
20
40
60
TIME (mins)

Fig. 6.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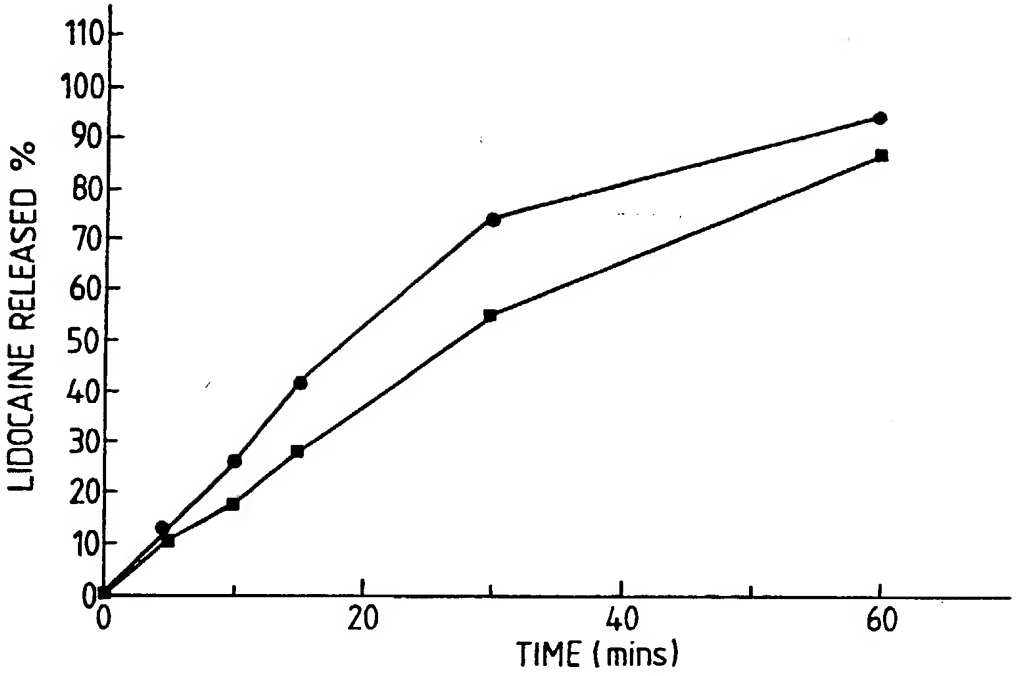
TIME (mins)

Fig. 7.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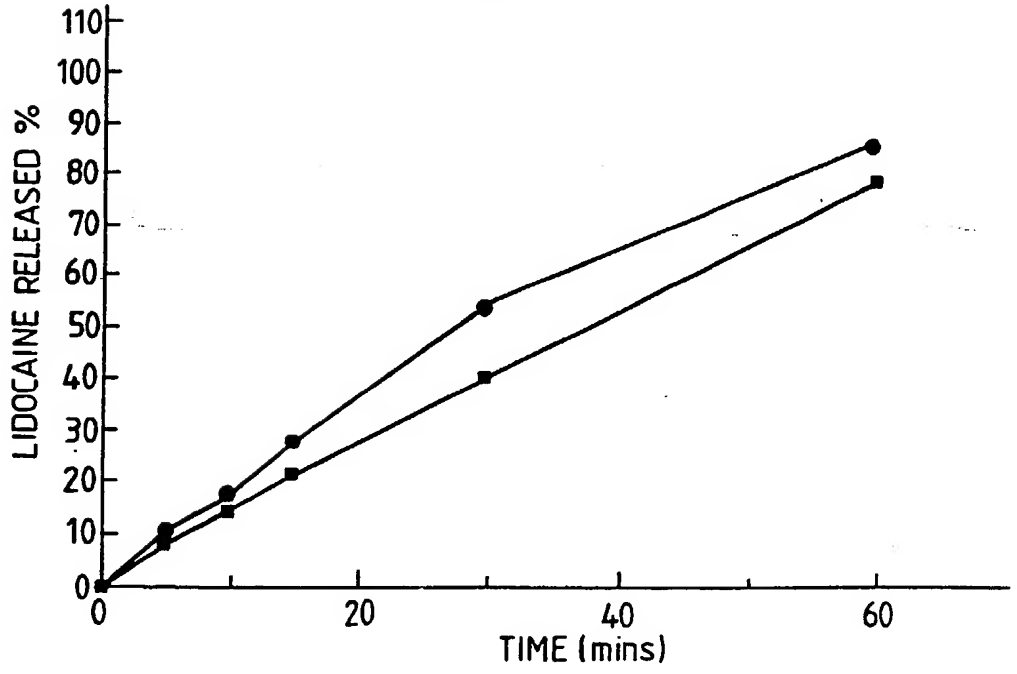
TIME (mins)

Fig. 8.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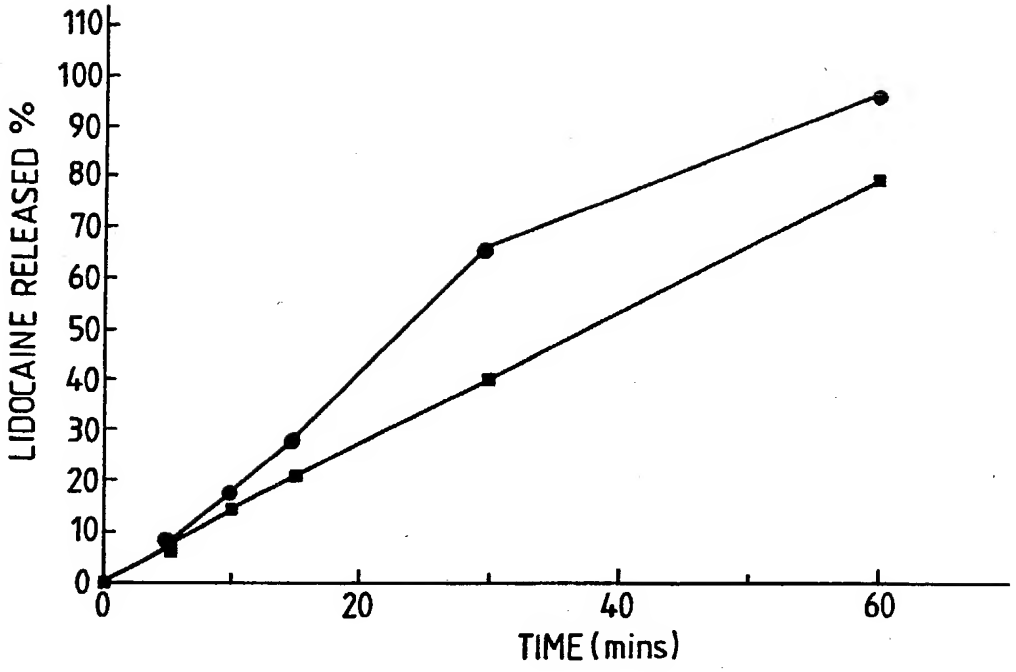
TIME (mins)

Fig. 9.


LIDOCAINE RELEASED %
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100
90
80
70
60
50
40
30
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10
0
0
20
40
60
TIME (mins)

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/00491

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/70

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	GB, A, 1108837 (ASTRA PHARMACEUTICAL PRODUCTS INC.) 3 April 1968, see the whole document	1-9
X	EP, A, 0200508 (NITTO ELECTRIC IND. CO. & SUNSTAR INC.) 10 December 1986, see the whole document, in particular column 21, example 3; columns 41,42, example 31	1-9
X	EP, A, 0250187 (JOHNSON & JOHNSON PROD.INC.) 23 December 1987, see the whole document, in particular page 3, lines 32-35	1-5,7-9

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* Special categories of cited documents: [14]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18th July 1989	- 8. 08. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 10, because they relate to subject matter not required to be searched by this Authority, namely:

pls. see Rule 39.1 (iv) - PCT:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8900491

SA 28467

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/08/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 1108837		BE-A-	690383	29-05-67
		DE-A-	1617282	06-02-75
		FR-M-	6733	24-02-69
		LU-A-	52460	25-06-68
		NL-A-	6616878	31-05-67
EP-A- 0200508	05-11-86	JP-A-	61249472	06-11-86
		JP-A-	61249473	06-11-86
		US-A-	4772470	20-09-88
EP-A- 0250187	23-12-87	US-A-	4713243	15-12-87
		AU-A-	7415587	17-12-87
		JP-A-	63019152	26-01-88

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 9/70	A1	(11) International Publication Number: WO 89/10740
		(43) International Publication Date: 16 November 1989 (16.11.89)

(21) International Application Number: PCT/GB89/00491

(22) International Filing Date: 9 May 1989 (09.05.89)

(30) Priority data:
8810951.7 9 May 1988 (09.05.88) GB

(71) Applicant *(for all designated States except US)*: INNOVATA BIOMED LIMITED [GB/GB]; 18 Dublin Street, Edinburgh EH1 3PT (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BOYES, Robert, Nichol [CA/GB]; 6 Lancaster Road, St Albans, Herts AL1 4ET (GB). PERKINS, Brenda [US/US]; 512 Avenue V, Birmingham, AL 35214 (US). STROBEL, Janna, N. [US/US]; 217 Honeybee Circle, Trussville, AL 35173 (US). DUNN, Richard, L. [US/US]; 1625 Sharp Point Drive, P.O. Box 460, Fort Collins, CO 80522 (US).

(74) Agents: WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU (GB).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB, GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: BUCCAL LOCAL ANAESTHETIC

(57) Abstract

An anaesthetic patch suitable for use in the mouth is disclosed, which comprises a biocompatible hydrophilic polymer matrix loaded with an anaesthetic, which matrix is capable of adhering directly to the oral mucosa without an adhesive, and an impermeable inert support membrane.

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BUCCAL LOCAL ANAESTHETIC

This invention relates to an anaesthetic patch for use in the mouth.

Local anaesthesia for dental procedures is usually provided by parenteral injection of a suitable local anaesthetic product such as lignocaine or prilocaine. In some cases, these drugs are formulated in ointments, creams, gels or aerosol sprays to be applied to the gums to provide local pain relief. All of these anaesthetic procedures have significant disadvantages from both a medical and a patient acceptance point of view. Parenteral injections are difficult to administer, are extremely uncomfortable for the patient, are occasionally associated with serious adverse reactions and, in general, the anaesthesia lasts for a prolonged period after the dental procedure, causing unpleasant numbness in the lips and tongue of the patient. The various topical products are rapidly removed from their site of application in the mouth by the saliva and, as a result, the duration of their effect is very short. Furthermore, the anaesthetic is free to diffuse throughout the mouth and, thereby, causes an unpleasant taste as well as discomforting numbness in the tongue.

According to the present invention there is provided an anaesthetic patch for use in the mouth, which patch comprises a film comprising a biocompatible, hydrophilic polymer matrix loaded with an anaesthetic, which matrix is capable of adhering directly to the oral mucosa without an adhesive and an impermeable inert support membrane.

Optionally the anaesthetic patch includes a third component in the form of a release liner, which is positioned over the loaded matrix to keep the matrix clean prior to use of the patch. This liner is removed immediately before application of the patch to the oral mucosa.

Typically the release liner comprises silicone-

treated paper.

It is therefore possible in accordance with the invention to provide a device which concentrates the local anaesthetic to a specific site on the gums and which does not allow drug to diffuse into the mouth in general. The patch may not only provide concentrated anaesthetic effect to the site of application but that effect can also continue until the device is removed. The patch may allow anaesthetic agent to penetrate the gingival mucosa and reach the nerves which transmit painful stimuli from the tooth. The patch can therefore be employed to provide anaesthesia for operative procedures of the gums as well as for restorative procedures of the teeth themselves.

The patch incorporates a film comprising a biocompatible, hydrophilic polymer matrix loaded with anaesthetic. The film should have good adhesive properties, i.e. good wet tack, as the patch must adhere directly to the oral mucosa through the surface of the film not provided with a backing material. Wet tack may be determined by pressing a moist finger onto the surface of the film and then observing the adhesion of the film to the finger.

Suitable polymers for the matrix include sodium carboxymethyl cellulose (CMC), poly(vinyl pyrrolidone) (PVP), copolymers of methyl vinyl ether and maleic anhydride such as Gantrez (trade mark) ES-225 and an acrylic latex such as Rhoplex (trade mark) NB-560. Preferred polymers are polymers from which soft and flexible films may be formed. Such films are most practical for use in the mouth. Preferred polymers are therefore PVP and copolymers of methyl vinyl ether and maleic anhydride. PVP's are generally used having molecular weights from 20000 to 700000, typically from 40000 to 360000, for example PVP-40, PVP K-60 and PVP K-90 having molecular weights of 40000, 160000 and 360000 respectively. The low molecular weight PVP K-29/32 (having a molecular weight of in the region of 30000) may also be used. Although polymers of lower

molecular weight have the potential to impart greater flexibility to the patch than those of higher molecular weight, PVP K-90 combines a satisfactory degree of flexibility with strength and is therefore particularly suitable.

A non-toxic plasticiser may be incorporated into the polymer matrix to improve the softness and flexibility of the final patch. Suitable plasticisers include sorbitol and glycerol. Glycerol is generally preferred since it has a higher solubility in the solvents used in the preparation of the anaesthetic-loaded patch. The plasticiser may be incorporated in any amount, within the limits of its solubility, and is typically used in an amount of from 0.01 to 15% of the total weight of the anaesthetic-loaded matrix. For example, sorbitol is suitably used in an amount of 0.5% by weight and glycerol is suitably used in an amount of 5% by weight.

When the polymer matrix of the patch comprises more than one polymer, for example two, it is possible for the second polymer to act as a plasticiser within the composition. One example of a patch within the invention comprises a polymer matrix consisting of the anaesthetic lidocaine, two PVP's (PVP K-90 and PVP K-29/32) and glycerol in a weight ratio of 25:45:25:5. The PVP K-29/32, having a lower molecular weight than the PVP K-90, acts as a plasticiser in addition to the glycerol.

The anaesthetic provided in the patch may be a local anaesthetic, although the patches can be employed to deliver systemic anaesthetics too. An amide anaesthetic may be employed such as lignocaine (lidocaine), prilocaine, carbocaine, bupivacaine or etidocaine. The anaesthetic may be employed in free form or in the form of an acid addition salt, typically the hydrochloride. In particular, lignocaine or lignocaine hydrochloride is used.

The support membrane of the patch is inert and impermeable. The membrane generally comprises polyurethane,

for example it is a polyester/polyurethane film or foam, and is typically coated with an acrylic adhesive. The anaesthetic-loaded polymer matrix adheres in this case to the acrylic adhesive coating which, in turn, is relatively impermeable to the anaesthetic. The side of the membrane opposite to that coated with adhesive presents a smooth, non-sticky surface to the oral cavity, protecting and supporting the patch as a whole. The support membrane may be formed by laminating an acrylic adhesive, such as TT5022-00 available from Semex Medical, Frazer PA, US to a polyurethane which is in the form either of a thin film or a slightly thicker foam. A maximum thickness for the polyurethane film is generally about 63.6 μm (2.5 mil) whereas for the foam the maximum thickness is generally 762μm (30 mil).

Alternatively a commercially available support membrane may be used. Particularly suitable is KM1354-00, from Semex Medical, a polyester/polyurethane film coated with an acrylic adhesive. This typically comes provided with a silicone-treated release liner which protects the adhesive side of the membrane. A further example of a suitable membrane is KM-1952, an acrylic adhesive/polyurethane foam also from Semex Medical.

The support membrane is impermeable so that water and saliva can not penetrate into the patch and thereby allow anaesthetic to leach out through the surface which does not adhere to the oral mucosa. The support membrane is therefore typically coterminous in area with the polymer matrix film loaded with anaesthetic. This has the additional effect of ensuring a unidirectional flow of anaesthetic into the tissue of the mouth to be anaesthetised.

The third, and optional, component in the patch of the present invention is a release liner which is placed over the anaesthetic-loaded matrix. The liner serves both to keep the matrix clean and to prevent individual patches

from adhering to each other when packaged. The liner is typically a silicone-treated paper and a suitable example is 3402 available from Semex Medical, Frazer, PA. This particular product comes provided with a support membrane, although it is not essential to the invention that the release liner be supplied together with a support membrane.

The anaesthetic is suitably incorporated in the polymer matrix in an amount of from 1 to 30% by weight. The proportions may vary in this range depending upon the type of anaesthesia it is desired to induce. For anaesthesia of soft tissue, therefore, the film typically incorporates from 2 to 15% by weight of anaesthetic. For anaesthesia of deep tissue, the film typically comprises from 15 to 25% by weight of anaesthetic. The amount of anaesthetic will also depend upon the potency of the anaesthetic, however. For lignocaine either as the free base or as the hydrochloride, for example, from 5 to 30 mg of anaesthetic may be incorporated per cm^2 of the surface area of a patch.

The patches of the invention are suitably prepared by casting. In a preferred method, which is both economical and continuous, a doctor blade is used. This method comprises dissolving the anaesthetic and the matrix polymer in an appropriate inert solvent such as water, ethanol or acetic acid. Ethanol is particularly suitable. The resulting solution is then placed at one end of a casting substrate and a doctor blade is moved across the solution for the length of the casting substrate to spread the solvent blend evenly over the casting substrate. The solvent then evaporates off.

The casting substrate may be either the support membrane itself or, alternatively, the release liner. It is particularly convenient to use the release liner as casting substrate and to attach the support membrane to the polymer matrix charged with anaesthetic in a subsequent step to form a complete patch.

The doctor blade used in this casting method may be

any length, for example about 20 cm (or approx 8 in). The height of the blade is generally adjustable. Altering the weight has the effect of varying the thickness of the film formed on the casting substrate. The thickness of the film contributes to determining the content of anaesthetic in the final patch.

Besides adjusting the height of the doctor blade, an alternative means of controlling the thickness of the film on the casting substrate is by adjusting the viscosity of the casting solution. This may be done, for example by varying the content of ethanol in the solution.

The softness and flexibility of the final patch is increased by incorporating one or more plasticisers into the casting solution. Examples of suitable plasticisers include glycerol, sorbitol and fructose. Glycerol is particularly suitable, and is typically used at a concentration of 5wt%.

As an alternative to the doctor blade method of casting, the solution comprising the matrix polymer and the anaesthetic dissolved in a suitable solvent is simply poured into an open container, whereupon the solvent evaporates off. The resulting film is then provided with a support membrane, typically by adhesion.

The patches may be of any appropriate size or shape. Typically they may range in size from 1 to 5 cm^2, preferably from 1 to 2 cm^2. They may be circular, oval, square or rectangular. The thickness of the patch excluding the release liner is generally from 0.1 mm to 0.5 mm, for example from 0.157 mm to 0.464 mm. Taking the release liner into account the overall thickness is typically from 0.2 mm to 0.7 mm, for example from 0.227 to 0.627.

In a first embodiment of the invention, the patch is about 1.3 x 2.5 cm in area and comprises, as support membrane, a polyurethane-containing film (such as KM 1354-00 from Semex Medical); an anaesthetic-releasing film comprising about 25 mg lidocaine, about 25 mg of a poly(vinyl-pyrrolidone) polymer (such as PVP K-90 from Semex

Medical) and about 25 mg of glycerol; and, as release liner, a silicone-treated paper of which a suitable example is 3402 from Semex Medical.

In a second embodiment, the patch differs from that of the first embodiment in that the anaesthetic releasing film comprises about 25 mg of lidocaine, about 32 mg of a PVP and about 14 mg of glycerol. This patch has less dry tack than the first.

In use, the patch is applied to the buccal mucosal or gingival region in need of anaesthetising. The patch adheres via the exposed surface of the polymer matrix film loaded with anaesthetic. Typically, the patch is positioned to cover the cervical margin of the tooth and its attached mucosa. It is therefore usually located away from the gingival margins.

The following Examples illustrate the invention. In the accompanying drawings:

Figure 1 shows the average cumulative fraction of lidocaine. HCl released from various films in the in vitro evaluation in Example 1;

Figure 2 shows the average cumulative fraction of lidocaine from various films in the in vitro evaluation in Example 2;

Figure 3 shows the average cumulative fraction of lidocaine released from PVP K-60 film in Example 2 which was sealed in polyurethane film or not;

Figure 4 shows the effect of a lidocaine.HCL-containing film on the electrical stimulation threshold of teeth in Example 3;

Figure 5 shows the in vitro release characteristics of lidocaine patches tested in Example 5, wherein the line marked ■ denotes the use of a buffer at pH 7.3 as receiving fluid and the line marked ▲ denotes pure water as the receiving fluid;

Figure 6 shows the in vitro release characteristics of lidocaine patches tested in Example 6, and neat lidocaine tested in the Comparative Example, wherein the line marked ● denotes neat lidocaine, the line marked ■ denotes a patch containing 5.5 mg lidocaine and ▲ denotes a patch containing 12.6 mg lidocaine;

Figure 7 shows the in vitro release characteristics of lidocaine patches tested in Example 7, wherein the line marked ● denotes a patch incorporating sorbitol as a plasticiser and ■ denotes a patch without plasticiser;

Figure 8 illustrates the in vitro release characteristics of patches wherein the lidocaine film has two different thicknesses: the line marked ● denotes a thickness of 0.030 cm and ■ denotes 0.044 cm; and

Figure 9 illustrates the in vitro release characteristics of patches of different surface area, wherein the line marked ● denotes a patch of 3.25 cm^2 and ■ denotes one of 1.00 cm^2.

Example 1: Preparation and in vitro evaluation of lidocaine.HCl-loaded films

Films containing lidocaine.HCl were prepared from sodium carboxymethyl cellulose (CMC), Gantrez ES-225, polycaprolactone (PCL), PVP-40 and PVP K-60 by solvent casting in an open container at 50°C or at room temperature. Film preparation consisted of dissolving 25% lidocaine.HCl and 75% of the polymeric excipient in either water, ethanol or acetic acid. The solution was poured into an open container that was lined with either Mylar (trade mark) or Teflon (trade mark). The solvent was evaporated at 50°C or at room temperature. Films prepared with PVP, PCL and Gantrez were soft and flexible, while those prepared from CMC were harder and more rigid. Dry or wet tack was determined by pressing either a dry or a moist finger onto the surface of the film and then observing the adhesion of the film to the finger. The results from the various films

are summarised in Table 1.

TABLE 1 : LIDOCAINE.HCL-LOADED[a] FILMS

Sample No. E088	Film-forming polymer	Film thickness,[b] mm	Dry tack	Wet tack
-37-1	Gantrez ES-225	0.781	No	Yes
-38-1	CMC	0.299	No	Yes
-39-1	PVP K-60	0.813	Yes	Yes
-40-1	PVP-40	ND[c]	No	Yes
-42-1	PCL	ND	No	No

[a] All films contained 25 wt% lidocaine.HCl.

[b] Film thickness was determined with a micrometer.

[c] ND = not determined.

In vitro release experiments were carried out in triplicate using 1 cm^2 samples of each film. Release from the films was allowed from only one surface by applying a poly(methyl methacrylate) (PMMA) backing to one side of the sample. The in vitro release of lidocaine.HCl was then determined by immersing the samples in separate containers of Sorensen's phosphate buffer. The sealed containers were incubated at 37°C and agitated at low speed in a shaker bath. Samples for analysis of lidocaine were removed at 5, 10, 20, 30 and 60 minutes. The quantity of lidocaine.HCl released was determined in these samples spectrophotometrically. Figure 1 shows the average cumulative fraction of lidocaine.HCl released from various films.

Example 2: Preparation and in vitro evaluation of lidocaine-loaded films

Films containing lidocaine were prepared from PCL, PVP-40, PVP K-60, PVP K-90, Gantrez ES-225 and Rhoplex N-560 by solvent casting with a high-speed centrifugal spin caster. The preparation of blends for film formation was the same as that described for lidocaine.HCl. The lidocaine/polymer solution was injected with syringe into a spin-casting cup that was 8.9 cm (3.5 in.) in diameter, 7.6 cm (3.0 in.) deep and Mylar- or Teflon-lined. The cup was rotated at 3600 rpm until the solvent had evaporated. Then, the cylindrical film was removed from the cup and cut transversely to give a uniform, rectangular film. A film of CMC and 25% of lidocaine film was also prepared by dissolving the lidocaine and CMC in an ethanol/water mixture and solvent casting as described in Example 1. The results from the various films are summarised in Table 2.

TABLE 2 : LIDOCAINE-LOADED[a] FILMS

Sample No. E088	Film-forming polymer	Film thickness,[b] mm	Dry tack	Wet tack
-18-1	PCL	0.678	No	No
-19-1	PVP-40	0.518	No	Yes
-20-1	CMC	ND[c]	No	Yes
-48-1	PVP K-60	0.627	No	Yes
-52-1	PVP K-90	0.510	No	Yes
-76-1	Gantrez ES-225	0.497	No	Yes
-82-1	Rhoplex N-560	ND	Yes	No

[a] All films contained 25 wt % lidocaine.

[b] Film thickness was determined with a micrometer.

[c] ND = not determined.

In vitro release experiments were carried on 1 cm^2 samples of each film except CMC and Rhoplex N-560 in the same way as in Example 1. To limit the release of lidocaine to one surface of the sample, the sample was secured to a PMMA backing or to a polyurethane film via a medical grade adhesive. Figure 2 shows the average cumulative fraction of lidocaine released from the films.

In order to make a useful anaesthetic device, it was essential to have an impermeable backing material for the drug-loaded film. An experiment was carried out in which the PVP K-60 film containing lidocaine was completely sealed in polyurethane film. Unsealed and sealed material was then subjected to in vitro release studies as described previously. The results are presented in Figure 3. These show that only negligible amounts of lidocaine were able to penetrate the polyurethane film.

Example 3: In vivo evaluation of lidocaine.HCl-loaded PVP K-60 films

The clinical benefits of these films were evaluated in a study involving 9 human volunteers. In each subject a lidocaine-containing film and a placebo film were placed on contralateral sites on the gingiva. The films remained in place for 30 minutes. Anaesthesia of the mucosa was evaluated using a sharp probe. Conduction anaesthesia of the teeth was evaluated by measuring the electrical stimulation threshold of an appropriate tooth. Data describing the onset and duration of the soft tissue anaesthesia are presented in Table 3. The effect of the lidocaine-containing film on the electrical stimulation threshold of the teeth is presented in the accompanying Figure 4.

TABLE 3 : Changes in soft tissue sensation.

Sensory change	Time mins	S.D. mins
Mucosa analgesic	7.4	3.4
Onset of lip paraesthesia	11.0	3.7
Return of normal sensation after patch removed		
Mucosa	26.4	8.9
Lip	22.6	5.2

It is clear from these data that the lidocaine-containing films with a polyurethane backing produce anaesthesia of the mucosa which is of considerable depth and rapid onset. Furthermore, this anaesthesia remains localized to the area of application, and the strong unpleasant taste of the drug is not observed. The observed changes in conduction threshold indicate that application of lidocaine films designed in this manner can produce varying degrees of conduction anaesthesia of the teeth.

Example 4: Preparation of lidocaine loaded film by doctor blade method of casting

Films comprising lidocaine as the anaesthetic were prepared from PVP K-90 and a combination of PVP K-90 and PVP K-29/32. Ethanol was used as the casting solvent and the casting substrate was either the release liner, or a support membrane comprising one or two layers of KM 1345-00, an acrylic adhesive/polyester polyurethane from Semex Medical.

The film was cast using a doctor blade in a fabrication box approx 76 cm x 35.5 cm x 15 cm (30" x 14" x 6") having a built-in manifold of five individually adjustable values to enable the flow rate and dispersion of nitrogen to be regulated. The composition of the casting solutions and the process conditions used are shown in Table 4.

TABLE 4

PREPARATION OF LIDOCAINE LOADED FILM BY DOCTOR BLADE METHOD OF CASTING

Sample	Composition of casting solution[a] wt % lidocaine/PVP[b]/plasticizer[c]	Process conditions: Casting substrate	Process conditions: Blade ht, mil
E088-132-03	25/75/0	Support membrane (1)[g]	
E088-133-01	25/75/0	Support foam[h]	130
E088-133-02	25/75/0	Support foam	90
E088-139-01	25/75/0	Support membrane (1)	75/75[j]
E088-140-01	10/90/0	Support membrane (1)	75/75
E088-142-01	25/74.5/0.5[k]	Support membrane (1)	75
E088-142-02	25/74.5/0.5[k]	Support membrane (1)	75
F092-011-01	25/70/5	Support membrane (2)	75
F092-013-01	25/75/0	Support membrane (2)	75/100
F092-020-01	25/72/3	Support membrane (2)	50/100
F092-022-01	25/74/1[k]	Support membrane (2)	50/100
F092-024-01	25/75/0	Support membrane (2)	50/100
F092-025-01	25/75/0	Release liner	100
F092-027-01	25/72/3	Support membrane (1)	75
F092-029-01	25/70/5	Support membrane (2)	75
F092-030-01	25/74/1[k]	Support membrane (2)	75
F092-043-01	25/(50:25)/0	Release liner	100
F092-044-01	25/(45:25)/5	Release liner	100
F092-045-01	50/50/0	Release liner	100
F092-046-01	50/45/5	Release liner	100
F092-047-01	25/(50:25)/0	Release liner	100
F092-048-01	25/(45:25)/5	Release liner	100
F092-049-01	50/50/0	Release liner	100
F092-050-01	50/45/5	Release liner	100
F092-053-01	25/75/0	Release liner	84
F092-056-01	50/45/5	Release liner	51
F092-056-02	50/45/5	Release liner	51
F092-057-01	50/45/5	Release liner	51
F092-058-01	50/45/5	Release liner	51
F092-059-01	50/45/5	Release liner	51
F092-060-01	50/45/5	Release liner	84
F092-065-01	25/(45:25)/5[m]	Release liner	84

TABLE 4 (continued)

Sample	N_2 flow rate, SCFH [d]	Drying time, hr [e]	Lidocaine-releasing film thickness, mm	Patch loading, [f] mg of lidocaine
E088-132-03	20	2	0.30	29
E088-133-01	20	2	ND[i]	ND
E088-133-02	20	2	0.18	16
E088-139-01	20	3	0.44	41
E088-140-01	20	3	0.48	18
E088-142-01	20	2	0.28	23
E088-142-02	20	2	0.23	15
F092-011-01	20	2	ND	ND
F092-013-01	20	4	0.39	39
F092-020-01	20	4	0.40	34
F092-022-01	20	4	0.31	21
F092-024-01	20	4	0.51	55
F092-025-01	20	2	0.41	36
F092-027-01	20	1	0.45	42
F092-029-01	20	1	0.28	27
F092-030-01	20	1	0.37	41
F092-043-01	4/10	6	0.45	78
F092-044-01	4/10	6	0.39	27
F092-045-01	4/10	6	0.39	77
F092-046-01	4/10	6	0.33	52
F092-047-01	10	2	0.39	38
F092-048-01	10	2	0.47	37
F092-049-01	10	2	0.53	78
F092-050-01	10	2	0.52	80
F092-053-01	10	2	0.29	25
F092-056-01	10	1	0.12	20
F092-056-02	10	1	0.16	35
F092-057-01	10	1	0.13	26
F092-058-01	10	3	0.13	20
F092-059-01	10	3	0.14	20
F092-060-01	10	2	0.40	50
F092-065-01	10	2	0.44	ND

Footnotes to Table 4

a Casting solutions contained 30 wt % solids (lidocaine, PVP, plasticizer) and 70 wt % ethanol, unless otherwise noted.

b PVP = PVP K-90 or a blend of PVA K-90 and PVP K-29/32 (w/w).

c Plasticizer = Glycerol, unless otherwise noted.

d SCFH = Standard cubic feet per hour.

e Rounded off to nearest hour.

f Lidocaine loading in a 3.25 cm^2 patch (1.3 x 2.5 cm). The lidocaine loading was calculated using the weight of the patch and the initial lidocaine concentration in the casting solution. (It was assumed that the patch did not contain residual ethanol.)

g Trade Name = KM1352-00 (Semex Medical, Frazer, PA), a polyurethane film coated with an acrylic adhesive. Number in parenthesis indicates number of layers.

h Trade Name = KM1952-00 (Semex Medical, Frazer, PA), a polyurethane foam coated with an acrylic adhesive.

i ND = Not determined.

j --/-- indicates two film layers were cast. The first layer was allowed to dry (about 1/2 the drying time), and then the second layer was cast on top of the first.

k Plasticizer = sorbitol.

l Casting solution contained 40 wt % solids and 60 wt % ethanol.

m Casting solvent was water, solids/water, 30:70 (w/w).

Example 5 In vitro evaluation of lidocaine patches produced by doctor blade casting

Patches loaded with 8.9 mg of lidocaine were suspended in purified water, at 37°C under infinite sink conditions, in an individual wire mesh cage to ensure that the lidocaine-loaded film was exposed at all times to the receiving fluid. Each sample was placed in an Eberbach shaker bath (Eherbach Corp; Ann Arbor, MI) and agitated at 60 or 120 oscillations per minute (OPM). Periodically the caged patches were transferred to fresh water. Samples of the water exposed to the patches (the receiving fluid) were quantified for lidocaine by UV spectophotometry.

The above-described process was repeated using Sorensen's phosphate buffer (pH = 7.3) instead of water as the receiving fluid.

Figure 5 shows the release kinetics of the lidocaine patches tested as described above. They are seen to be very similar.

Example 6: Effect on in vitro release kinetics of the loading of the patch

Patches 1 cm^2 in area were prepared by the method of Example 4, and were loaded with 12.6 mg or 5.5 mg of lidocaine (corresponding, respectively, to 25 wt% and 10 wt% of lidocaine in the film). Their in vitro release characteristics were evalluated by the process of Example 5, using deionised water at 37°C as the receiving fluid and an Eberbach shaker bath agitated at 60 oscillations per minute.

Figure 6 shows the dissolution profiles obtained. A change in the lidocaine loading appears to have little effect on the amount of lidocaine released from the patch.

Comparative Example: Release characteristic of neat lidocaine

Three samples of neat lidocaine, weighing 9.5 mg, 9.0 mg and 5.3 mg respectively were evaluated in vitro and

dissolution profiles established. The results are shown in Figure 5, from which a comparison with the dissolution profiles obtained with two loaded patches indicates that the polymer matrix in the patches is exercising a control over lidocaine release.

Example 7: Effect on in vitro release characteristics of lidocaine from a patch of a plasticiser

To illustrate the effect of a plasticiser on lidocaine release from a patch, two patches were prepared by the method of Example 4, one including the plasticiser sorbitol in the polymer matrix:

Lidocaine per patch (mg)	Sorbitol (mg)	(wt%)
4.6	0.46	0.5
8.9	0.00	0.0

Figure 7 shows that sorbitol slightly increases lidocaine release. However, sorbitol is not ideal since its low solubility in the casting solution makes it impossible to incorporate more than 1% by weight in the patch. Glycerol has proved to be a preferably plasticiser since it may readily be incorporated in higher concentrations, typically 5% by weight.

Example 8: Effect of the lidocaine-releasing film thickness on in vitro release characteristics

Patches 1 cm^2 in area were prepared by the method of Example 4.

Patch	Lidocaine per patch (mg)	Film thickness (cm)
1	8.9	0.030
2	12.6	0.044

They were tested by the process of Example 5 using deionised water at 37°C as receiving fluid and a shaker bath agitated at 60 oscillations per minute.

Figure 8 shows the dissolution profiles obtained, which indicate that a decrease in film thickness leads to an increase in lidocaine release. The difference in this particular instance appears to be only slight, although overall the thickness of the lidocaine film is observed to be one of the most important parameters in determining the total dose of lidocaine from a patch.

Example 9: Effect of surface area on release characteristics

Two patches of different surface area were prepared by the method of Example 4, as follows:

Patch	Surface area (cm^2)	Lidocaine loading (mg)
1	3.25 (1.3x2.5cm)	41.0
2	1.00 (1.00x1.00cm)	12.6

Their in vitro release characteristics were determined by the process of Example 5, using deionised water at 37°C as the receiving fluid and a shaker bath agitated at 60 oscillations per minute.

The results are shown in Figure 9, from which it is seen that an increase in surface area leads, as might be expected, to an increase in lidocaine release.

CLAIMS

1. An anaesthetic patch suitable for use in the mouth, which comprises a biocompatible hydrophilic polymer matrix loaded with an anaesthetic, which matrix is capable of adhering directly to the oral mucosa without an adhesive, and an impermeable inert support membrane.

2. An anaesthetic patch according to claim 1 which includes a release liner positioned over the matrix loaded with anaesthetic.

3. An anaesthetic patch according to claim 1 wherein the impermeable inert support membrane is coterminous in area with the matrix loaded with anaesthetic.

4. An anaesthetic patch according to claim 1 wherein the polymer matrix includes one or more plasticisers.

5. An anaesthetic patch according to claim 4 wherein the polymer matrix includes glycerol or sorbitol.

6. An anaesthetic patch according to claim 1 wherein the polymer matrix comprises poly(vinylpyrrolidone) or a copolymer of methyl vinyl ether and maleic anhydride.

7. An anaesthetic patch according to claim 1 wherein the anaesthetic is lidocaine or lidocaine hydrochloride.

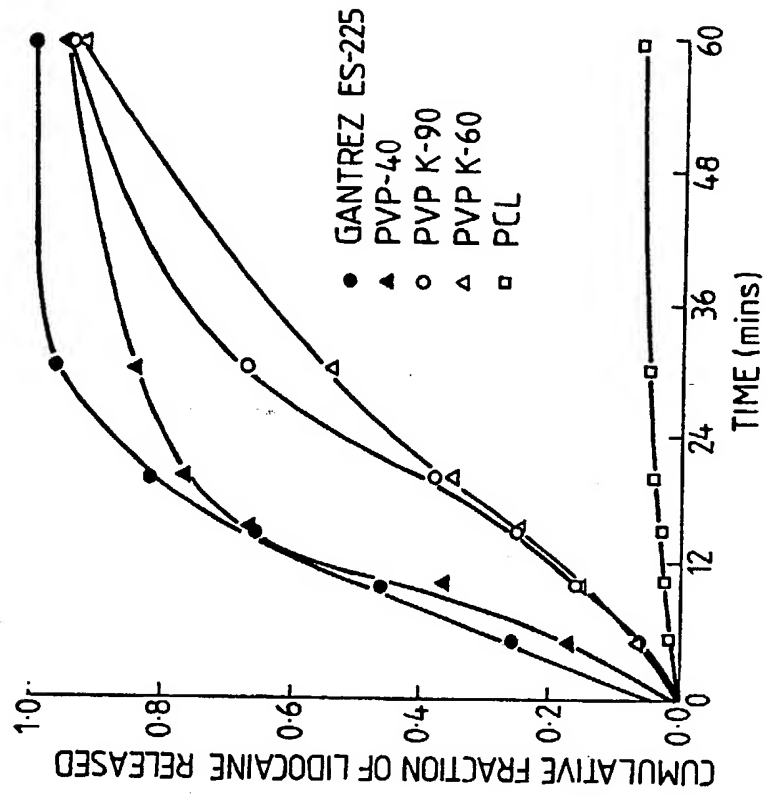
8. A method for producing an anaesthetic patch as claimed in claim 1 which comprises dissolving the anaesthetic and the hydrophilic polymer matrix in an inert solvent, spreading the resulting solution on a casting substrate by means of a blade and allowing the solvent to evaporate off.

9. A method according to claim 8 wherein the casting substrate is the release liner and wherein the support membrane is attached to the side of the loaded polymer matrix opposite to the release liner in a subsequent step.

10. A method of anaesthetising the buccal mucosa or the gingival region in a human or animal patient which

comprises applying to the mucosae or region in need of anaesthetising an anaesthetic patch as claimed in any one of claims 1 to 8, or a patch produced by the method as claimed in claim 9.

Fig. 2.


GANTREZ ES-225
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PVP K-90
PVP K-60
PCL
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TIME (mins)
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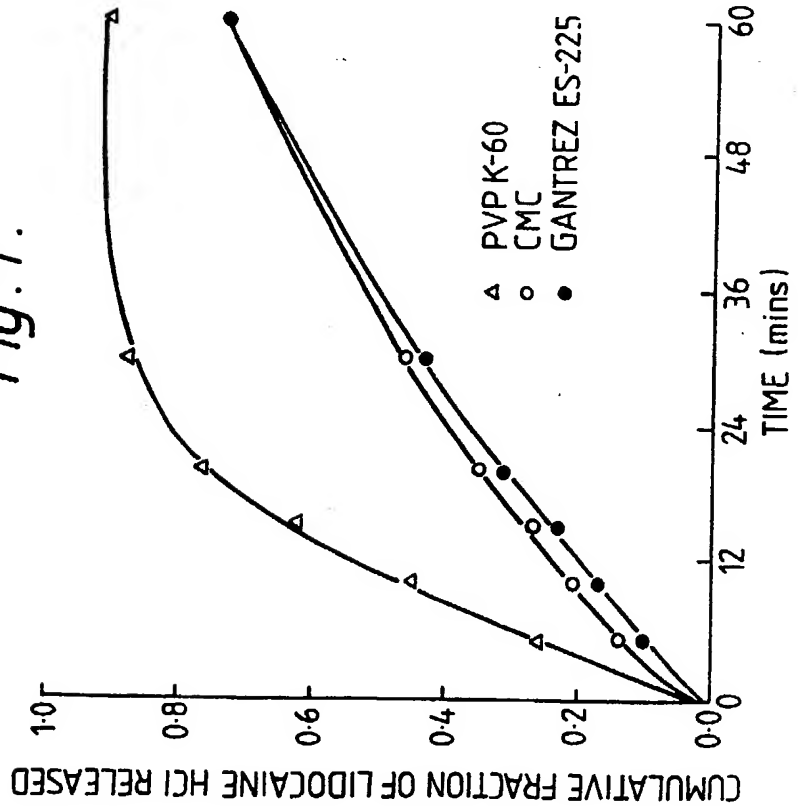
0·2
0·4
0·6
0·8
1·0
0
12
24
36
48
60

Fig. 1.


PVP K-60
CMC
GANTREZ ES-225
CUMULATIVE FRACTION OF LIDOCAINE HCl RELEASED
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0·4
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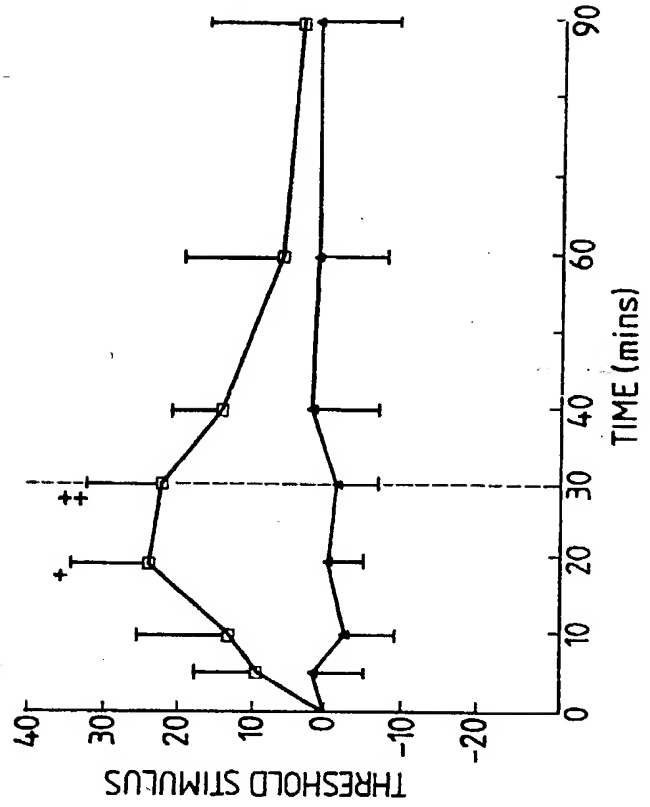
0·8
1·0
0
12
24
36
48
60

Fig. 4.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20
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-10
-20
+
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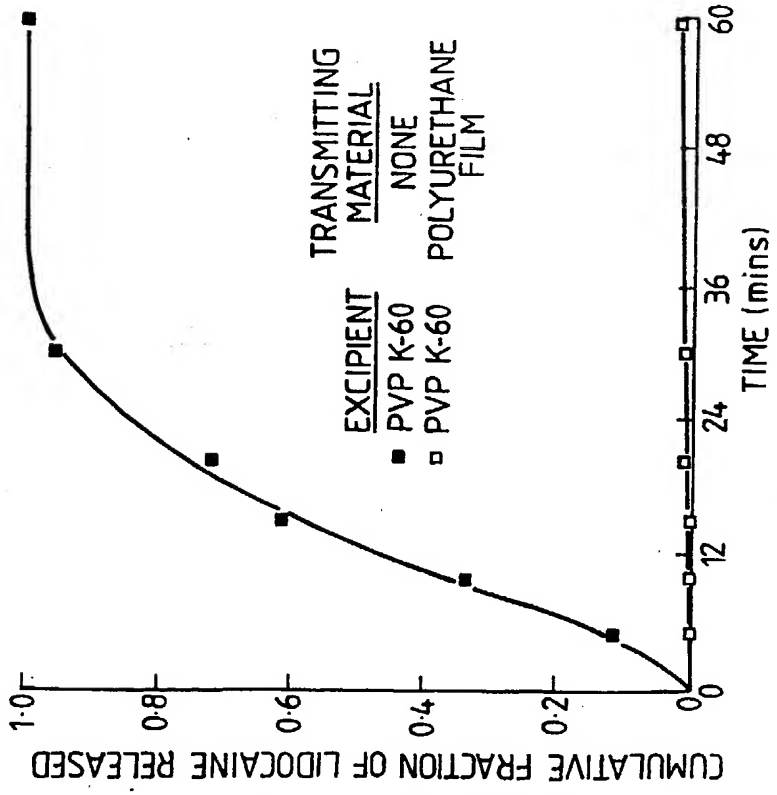
TIME (mins)

Fig. 3.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12
24
36
48
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TIME (mins)
EXCIPIENT
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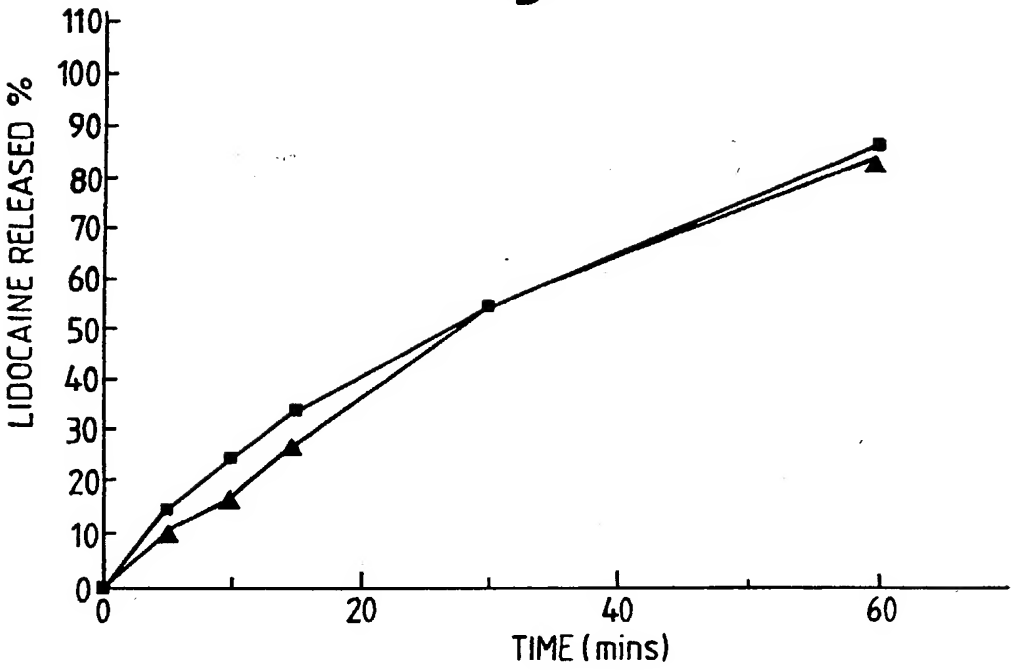
TRANSMITTING MATERIAL
NONE
POLYURETHANE FILM

Fig. 5.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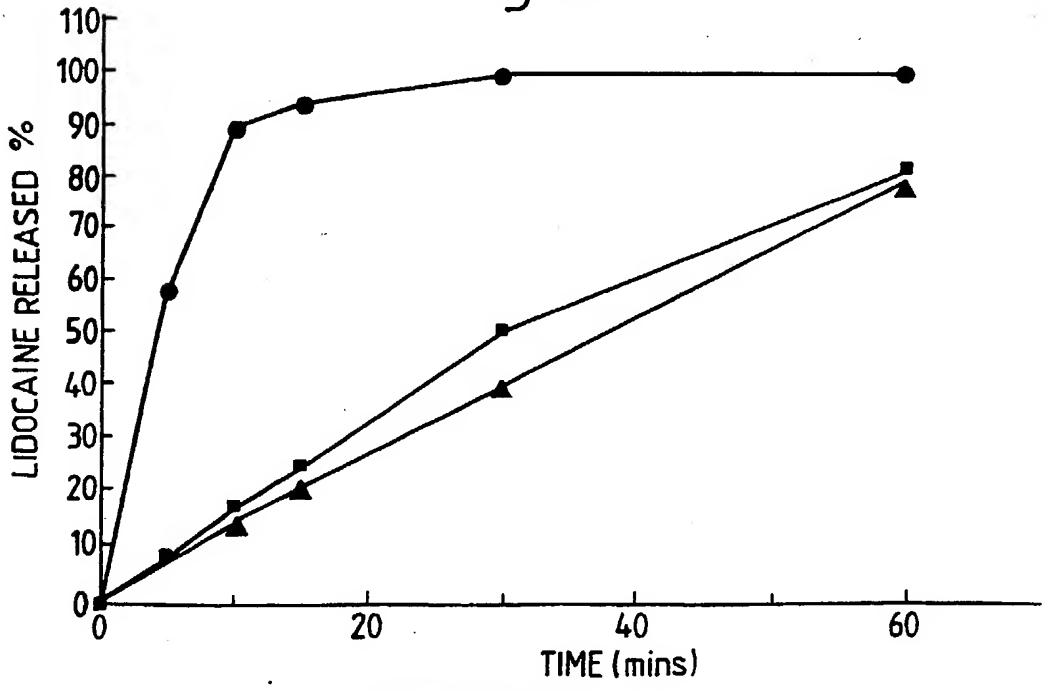
TIME (mins)

Fig. 6.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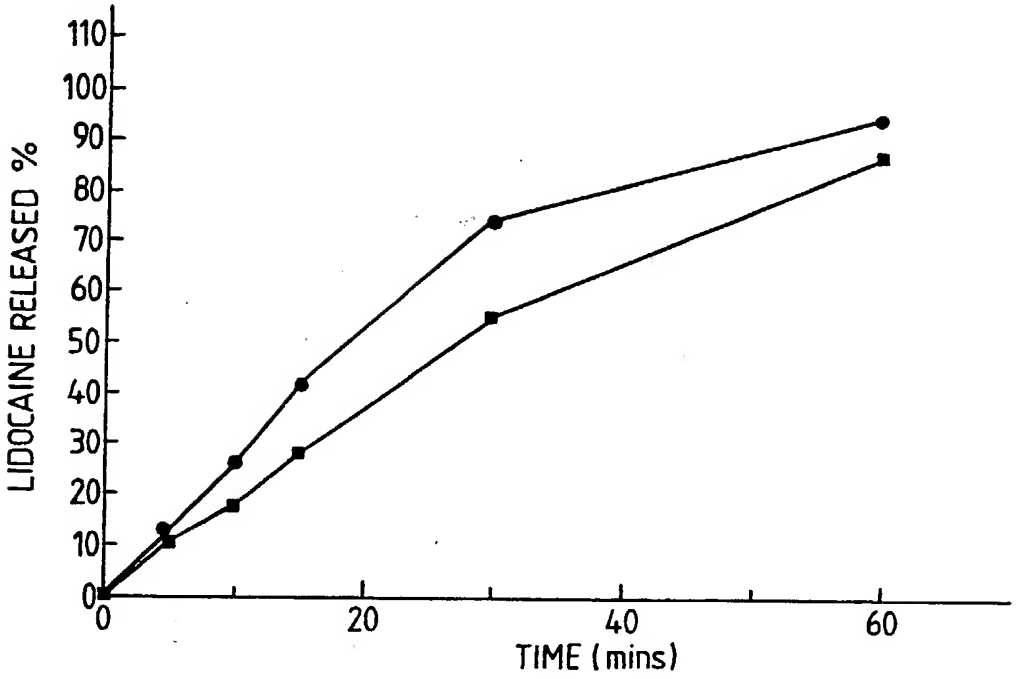
TIME (mins)

Fig. 7.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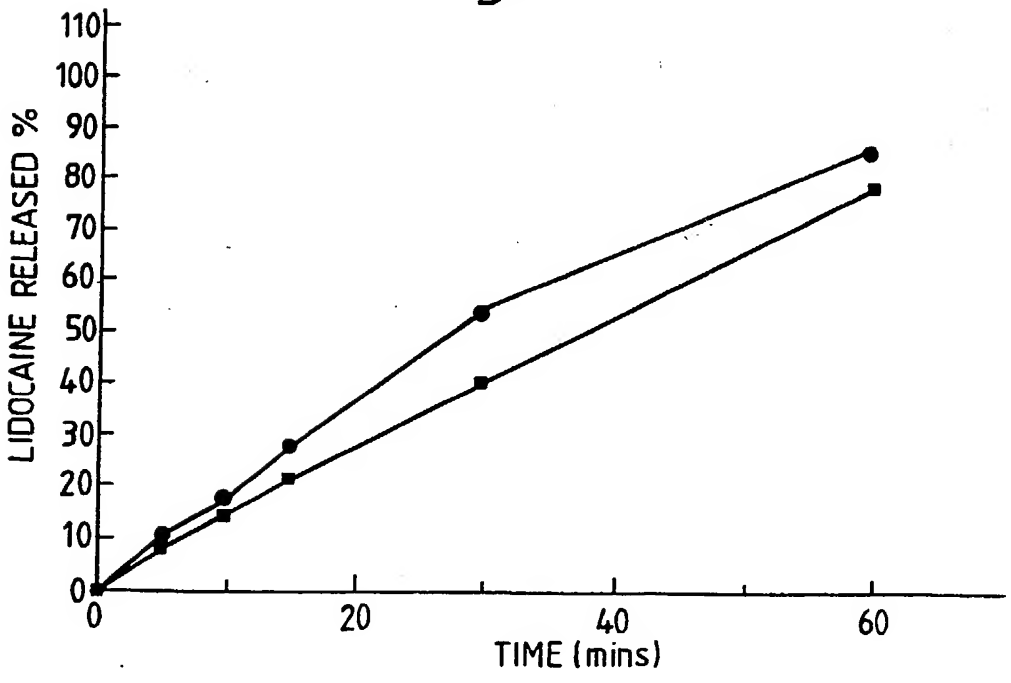
TIME (mins)

Fig. 8.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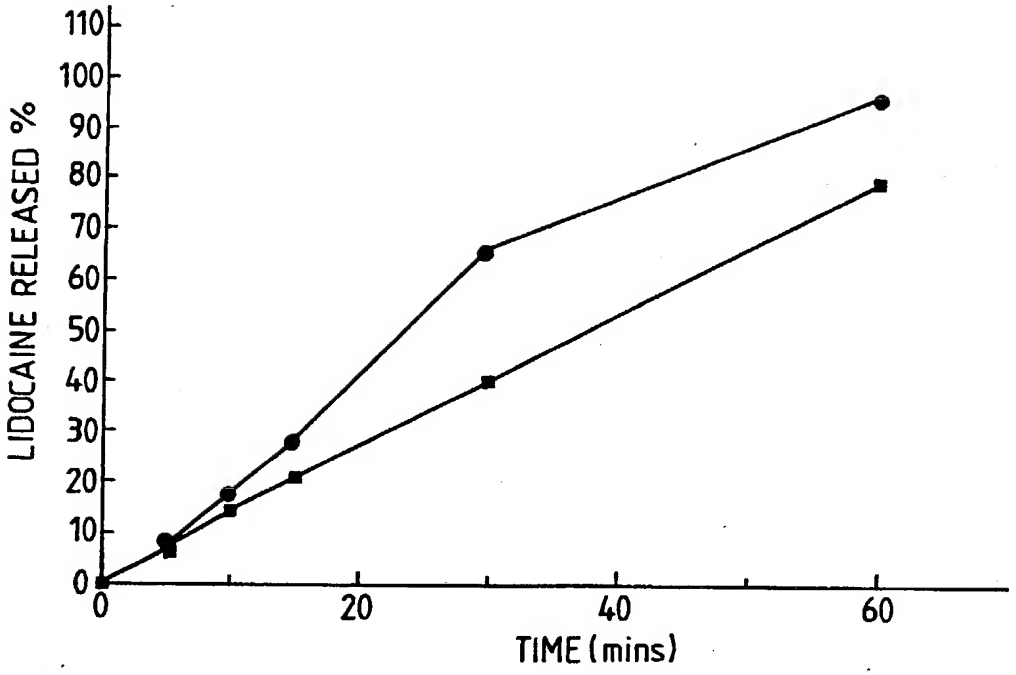
TIME (mins)

Fig. 9.


LIDOCAINE RELEASED %
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20
40
60
TIME (mins)

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/00491

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/70

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	GB, A, 1108837 (ASTRA PHARMACEUTICAL PRODUCTS INC.) 3 April 1968, see the whole document	1-9
X	EP, A, 0200508 (NITTO ELECTRIC IND. CO. & SUNSTAR INC.) 10 December 1986, see the whole document, in particular column 21, example 3; columns 41,42, example 31	1-9
X	EP, A, 0250187 (JOHNSON & JOHNSON PROD.INC.) 23 December 1987, see the whole document, in particular page 3, lines 32-35	1-5,7-9

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* Special categories of cited documents: [14]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18th July 1989	- 8. 08. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 10, because they relate to subject matter not required to be searched by this Authority, namely:

pls. see Rule 39.1 (iv) - PCT:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8900491

SA 28467

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/08/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 1108837		BE-A-	690383	29-05-67
		DE-A-	1617282	06-02-75
		FR-M-	6733	24-02-69
		LU-A-	52460	25-06-68
		NL-A-	6616878	31-05-67
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		AU-A-	7415587	17-12-87
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